Correspondence

Generalized bullous fixed drug eruption after Oxford–AstraZeneca (ChAdOx1 nCoV-19) vaccination

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Dear Editor,

A 74-year-old Thai man presented with a rash that had appeared 25 h after he had received his first dose of the adenoviral-vectored COVID-19 vaccine, ChAdOx1 nCoV-19 (Oxford–AstraZeneca). The lesions had appeared abruptly without any accompanying symptoms. The patient's medical history included end-stage renal disease, atrial fibrillation and ischaemic stroke. The patient denied taking any new drugs, supplements or foods prior to this cutaneous eruption.

Physical examination revealed multiple, well-defined, round to oval, erythematous to violaceous plaques with central dusky appearance and bullous formation on the trunk and both extremities (Fig. 1). There was no mucosal involvement.

A punch biopsy was taken, and histopathology findings were consistent with bullous fixed drug eruption (BFDE) (Fig. 2).

Laboratory investigations did not show any definite internal organ involvement.

Given the clinical and histological features, a diagnosis of generalized BFDE (GBFDE) was made. Fixed drug eruption (FDE) (not bullous or generalized) typically presents within 1–2 weeks after the initial exposure, and in < 2 days for subsequent episodes, whereas GBFDE occurs with more sudden onset and typically within 24 h.[1] Based on the temporal relationship, the ChAdOx1 nCoV-19 vaccine was considered as the eruption trigger, with a score of 5 (probable) on the Naranjo Adverse Drug Reaction Probability Scale.

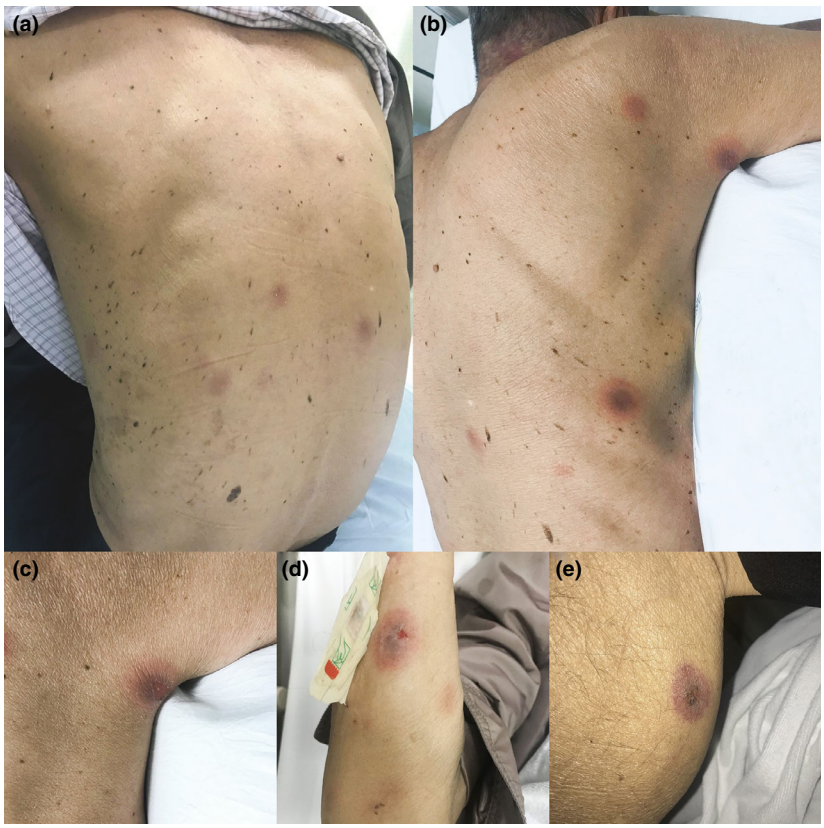

Figure 1 (a,b,d) Round to oval, erythematous to violaceous patches with central dusky appearance on the trunk and limbs; (c,d,e) large and well-demarcated central erosions were also noted on (c) the axilla and trunk; (d) right forearm and (e) right leg. No mucosal lesions were observed and the lesions were found in > 2 different sites of the body.

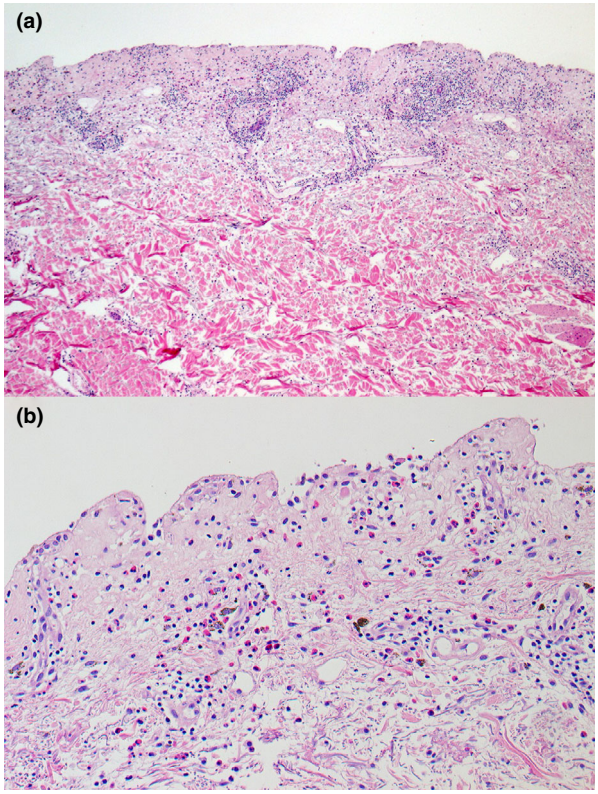

Figure 2 (a,b) Histological examination of a punch biopsy was performed from the lesion on the patient's back showed (a) subepidermal separation with superficial and deep perivascular inflammatory cell infiltration and (b) mixed inflammatory cells infiltrate, composing of lymphohistiocytes and numerous eosinophils. Melanophages were seen in the upper dermis. Haematoxylin and eosin, original magnification (a) × 50; (b) × 200.

Several vaccines have been implicated in triggering FDE, including the combined pentavalent DTaP-IPV-Hib (6-in-1) vaccine, yellow fever, influenza, human papillomavirus, recombinant adjuvant varicella zoster vaccine, and COVID-19 vaccines.[2–5] Whereas FDE is usually self-limiting and has a favourable prognosis, GBFDE is considered a severe cutaneous adverse reaction (SCAR) with a high mortality rate among elderly patients.[1] Despite the wide use of the COVID-19 vaccinations, only eight cases of SCAR associated with these vaccines have been documented (Table 1).

The treatment for GBFDE treatment is cessation of the causative agents and supportive care.[1] We treated our patient with topical 0.25% desoximetasone cream. The lesions gradually resolved within 2 weeks, leaving postinflammatory hyperpigmentation.

Use of patch testing on an area of residual hyperpigmentation after FDE resolution was considered as a method to confirm the culprit drug; unfortunately, testing could not be performed due to limited access to the vaccine and hospital areas during the COVID-19 pandemic. As an alternative, an interferon (IFN)-γ ELISpot assay was undertaken. This technique assesses the amount of IFN-γ production from peripheral blood mononuclear lymphocytes after stimulation with the suspect agents. In this case, the vaccine excipient, polysorbate80 (dilutions of 1 : 2000 and 1 : 10 000), was tested and yielded negative results. Our patient also reported receiving an annual influenza vaccination, which contains a similar excipient (polysorbate), without any adverse reactions. This indicated that the GBFDE was a result of a hypersensitivity reaction to the ChAdOx1 nCoV-19 vaccine rather than the excipient.

To our knowledge, this is the first report of ChAdOx1 nCoV-induced GBFDE. Because of the potential recurrence of SCAR, the patient was advised to switch to a different COVID-19 vaccine platform.

Acknowledgement

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Table 1 Reported cases of severe cutaneous adverse reactions due to COVID-19 vaccine administration.

Patient	Sex	Age, years	Allergy	Vaccine platform	Dose	Timing of onset	Lag period after vaccination, days, days	Clinical phenotype	Supporting investigations	Outcome	Second dose administration
1	M	74	Sulfa drugs, amoxicillin–clavulanic acid	Viral vector vaccine (Janssen, Ad26.COV2.S)	First	3 days	10	AGEP	Blood test: leucocytosis with neutrophilia and eosinophilia, normal creatinine level and liver enzymes Histology: epidermal spongiosis with subcorneal neutrophilic pustules and dermal neutrophilic inflammation with eosinophils. DIF: negative	Improved with oral prednisolone 20 mg/day and topical steroid	NA
2	F	43	NA	Viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	3 days	NA	AGEP	Blood test: leucocytosis with eosinophilia. Histology: lichenoid interface dermatitis, intracorneal pustules, lymphocytic infiltrate with numerous eosinophils	Resolution with topical corticosteroid within 30 days	Platform changed to mRNA vaccine (Pfizer/BioNTech, BNT162b2); no recurrence of reaction
3	F	32	No	Viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	3 weeks	NA	AGEP	Blood test: leucocytosis with neutrophilia	Resolution with short course systemic corticosteroid within 2 weeks	Not mentioned
4	M	38	NA	mRNA vaccine (Pfizer/BioNTech, BNT162b2)	Second	5 days	NA	AGEP	Blood test: marked neutrophilia Histology: supportive of the diagnosis of AGEP	Resolution with topical mometasone cream	NA
5	M	60	NA	Viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	3 days	7	SJS	Histology: moderate intraepidermal infiltration of lymphocytes and neutrophils with moderate spongiosis, scattered degenerated apoptotic keratinocytes, patchy areas of basal cell degeneration and interface dermatitis, perivascular and periadnexal inflammatory cell infiltrate along with extravasation of erythrocytes in dermis	Complete resolution with oral ciclosporin 300 mg/day after 7 days	Platform changed; no data on outcome

Table 1 continued

Patient	Sex	Age, years	Allergy	Vaccine platform	Dose	Timing of onset	Lag period after vaccination, days, days	Clinical phenotype	Supporting investigations	Outcome	Second dose administration
6	F	Middle-aged	No	mRNA vaccine (Pfizer/BioNTech, BNT162b2)	Second	5 days	NA	SJS	NA	Treated with oral prednisolone 30 mg/day; outcome unknown	NA
7	F	49	NA	mRNA vaccine (Pfizer/BioNTech, BNT162b2)	First	7 days	NA	TEN	Histology: full-thickness epidermal necrosis along with dermal–epidermal separation and necrotic keratinocytes	Treatment with 2 doses of etanercept 50 mg/mL (on Days 1 and 3); complete resolution in 22 days	Not mentioned
8	M	66	No	mRNA vaccine (Moderna, mRNA-1273)	Second	24 h	5	GBFDE	Blood test: anti-BP180 negative (8), anti-BP230 negative (< 2) Histology: full-thickness epidermal necrosis and a very sparse lymphocytic inflammatory infiltrate	Improved with high-dose oral prednisone	NA
9 (our case)	M	74	Penicillin (swollen lips)	Viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	25 h	2	GBFDE	Histology: subepidermal separation with superficial and deep perivascular mixed inflammatory cells infiltration composing lymphohistiocytes and numerous eosinophils, melanophages were seen in the upper dermis IFN-γ ELISpot assay: negative for polysorbate 80	Resolution with residual hyperpigmentation with topical desoximetasone within 2 weeks	Platform changed; no data on outcome

AGEP, acute generalized exanthematous pustulosis; BP, bullous pemphigoid; DIF, direct immunofluorescence; GBFDE, generalized bullous fixed drug eruption; IFN, interferon; NA, not applicable; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.